Original Article

Age and clinical spectrum of COVID-19 are associated with safety of transarterial chemoembolization in hepatocellular carcinoma: a retrospective cohort study

Zizhuo Wang[#]^, Tingting Yang[#], Lijie Zhang^, Joyman Makamure, Wei Hong, Bin Liang^

Department of Radiology, Hubei Key Laboratory of Molecular Imaging, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Contributions: (I) Conception and design: Z Wang, T Yang; (II) Administrative support: B Liang; (III) Provision of study materials or patients: Z Wang, T Yang, L Zhang; (IV) Collection and assembly of data: J Makamure; (V) Data analysis and interpretation: Z Wang, T Yang, W Hong; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work as co-first authors.

Correspondence to: Bin Liang, MD, PhD. Department of Radiology, Hubei Key Laboratory of Molecular Imaging, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1277 Jiefang Road, Wuhan 430022, China. Email: bliang@hust.edu.cn.

Background: Hepatocellular carcinoma (HCC) patients with coronavirus disease 2019 (COVID-19) undergoing open surgery show increased adverse events (AEs) and mortality, while the safety of transarterial chemoembolization (TACE) in coinfected patients remains understudied, limiting available evidence. This study aims to investigate the safety of TACE in HCC patients coinfected with COVID-19, and to explore the potential risk factors affecting the occurrence of serious AEs (SAEs), thus providing evidence for clinical treatment strategies in such patients.

Methods: This retrospective study involved HCC patients who underwent TACE with or without COVID-19 infection at our institution from November 2022 to February 2023. Quantitative reverse transcription-polymerase chain reaction (qRT-PCR) was used for the diagnosis of COVID-19. Patients were divided into an infected group (diagnosed with COVID-19 within 2 weeks before or after the procedure) and an uninfected group (tested negative for COVID-19). SAEs were ascertained according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. Logistic regression analysis of multiple clinical factors in preoperative baseline characteristics was performed to identify risk factors that might predict the occurrence of SAEs.

Results: A total of 118 patients (73 in the infected group, 45 in the uninfected group) were included, of whom 83.9% were male (86.3% in the infected group *vs.* 80.0% in the uninfected group) and the median age was 55.9±12.4 years (56.8±12.3 *vs.* 54.5±12.7 years). The clinical spectrum of COVID-19 in the infected group were 80.8% mild, 13.7% moderate, 1.4% severe and 4.1% critical. Sixteen of the 118 patients experienced SAEs (19.2% *vs.* 4.4%, P=0.046). The predominant SAEs were respiratory system diseases (9.6% *vs.* 0.0%) and liver damage (2.7% *vs.* 2.2%). In the univariate analysis, infection status [odds ratio (OR): 5.102, P=0.04, 95% confidence interval (CI): 1.102–23.627], gender (OR: 2.857, P=0.09, 95% CI: 0.862–9.468), age (OR: 1.061, P=0.03, 95% CI: 1.007–1.118) and clinical spectrum of COVID-19 (OR: 4.259, P<0.001, 1.943–9.336) were considered as the potential risk factors of grade ≥3 AEs. In multivariate analysis, younger age (OR: 1.064, P=0.044, 95% CI: 1.002–1.131) and a milder clinical spectrum of COVID-19 (OR: 5.736, P=0.004, 95% CI: 1.772–18.568) were independent factors associated with a lower occurrence of SAEs.

Conclusions: TACE in HCC patients co-infected with COVID-19 was considered relatively safe. Age and clinical spectrum of COVID-19 were associated with SAEs in HCC patients treated with TACE.

^ ORCID: Zizhuo Wang, 0009-0002-1690-8673; Lijie Zhang, 0000-0002-6296-2219; Bin Liang, 0000-0002-6130-8629.

Keywords: Transarterial chemoembolization (TACE); hepatocellular carcinoma (HCC); coronavirus disease 2019 (COVID-19); adverse events (AEs); safety

Submitted Jul 10, 2024. Accepted for publication Nov 22, 2024. Published online Dec 28, 2024.
doi: 10.21037/jgo-24-527
View this article at: https://dx.doi.org/10.21037/jgo-24-527

Introduction

The emergence of coronavirus disease 2019 (COVID-19) in recent years has presented a significant threat to the global population. COVID-19 infection may result in damage to the cardiovascular system (1), liver (2,3) and even multiple organ systems (4). The outbreak of the epidemic has adversely affected many surgeries, and patients with prior COVID-19 have a higher rate of postoperative adverse events (AEs) and mortality (5,6). In most Western countries, many medical procedures, including some loco-regional ones, have been postponed during the COVID-19 pandemic. This decision stems from the aim to mitigate risks associated with inducing immunosuppression, especially in patients affected by COVID-19. The American Society of Anesthesiologists (ASA) and Anesthesia Patient Safety Foundation expert consensus statement (7) recommends delaying elective surgery for 4 weeks or more based on the severity of symptoms after COVID-19. Surgery should be postponed by 7 weeks for patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (8). Since November 2022, the Chinese government has changed the epidemic prevention and control policy, and an increasing number of cancer patients with concurrent positive COVID-19 tests have been admitted to the hospital for scheduled surgical treatment.

Hepatocellular carcinoma (HCC) is one of the most common types of liver tumors globally and is the most common cause of cancer death, often developed on the background of chronic liver diseases such as cirrhosis or hepatitis virus infection (9,10). Patients with underlying medical comorbidities or cancer were at greater risk for contracting COVID-19 and are more likely to experience severe symptoms (11-17). Currently, only a small number of HCC patients are eligible for curative treatment such as resection, liver transplantation and ablation (18,19). For such patients, transarterial chemoembolization (TACE) has been recommended to control tumor growth and prolong survival (20-22). TACE is a minimally invasive operation, which has many advantages over traditional surgery, such as minimal invasiveness, faster recovery, shorter hospital stays and lower incidence of AEs. However, limited research aiming at evaluating the safety of TACE in HCC patients coinfected with COVID-19 has been conducted because of the indeterminacy decisions to postpone non-urgent interventional procedures. There is still poor evidence concerning the safety of performing TACE in patients with HCC who also have concurrent COVID-19 infection and whether TACE should be postponed in such patients.

The global impact of COVID-19 has evolved, but the virus continues to pose significant health challenges due to its potential to cause long-term multi-organ impairment. Even after recovery from the acute phase, patients may experience persistent damage to the cardiovascular system, liver, and other organs (23). This is particularly concerning for HCC patients, who often have pre-existing liver dysfunction due to cirrhosis or hepatitis virus infection. In this study, we aimed to assess the safety of TACE in HCC

Highlight box

Key findings

- The incidence of respiratory complications and mortality rate in the infected group were both lower than the results of previous studies. Additionally, age and the clinical spectrum of coronavirus disease 2019 (COVID-19) in hepatocellular carcinoma (HCC) patients treated with transarterial chemoembolization (TACE) were correlated with serious adverse events (SAEs).

What is known and what is new?

- In HCC patients co-infected with COVID-19, undergoing open surgery has shown a significantly higher incidence of adverse events (AEs) and mortality.
- This manuscript adds the safety of TACE in HCC patients with COVID-19.

What is the implication, and what should change now?

- The safety of TACE in HCC patients with peri-procedural COVID-19 was deemed acceptable. However, HCC patients with COVID-19 may be more likely to develop AEs or SAEs compared to those without COVID-19, which may demonstrate the need of extra attention for the HCC patients infected with COVID-19 receiving TACE treatment.

patients with concomitant COVID-19 and to explore the potential risk factors affecting the occurrence of serious AEs (SAEs) after TACE. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-527/rc).

Methods

Patients

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (IORG No. IORG0003571). Each participant provided their consent to participate. The medical records of HCC patients treated with TACE who were never infected with COVID-19 or infected with COVID-19 within 2 weeks before and after operation were reviewed in our institution between November 2022 and February 2023. Patients were grouped according to whether they were infected with COVID-19 and the timing of infection (within 2 weeks before and after TACE).

The eligibility criteria for the present study were as follows: (I) age 18 years or older; (II) diagnosed with HCC histologically or clinically according to the European Association for the Study of the Liver (EASL) guidelines; (III) treated with TACE during the study period; (IV) Barcelona Clinical Liver Cancer (BCLC) stage A–C; (V) Child-Pugh grade A or B without presence of uncontrollable ascites or hepatic encephalopathy; and (VI) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

The exclusion criteria were: (I) received other treatments, including hepatic arterial infusion chemotherapy (HAIC), radiotherapy, ablation, and systemic therapy during the same period; (II) without COVID-19 test or not infected within 2 weeks before or after TACE; (III) patients who had other concurrent malignancies or a history of other malignancies; and (IV) incomplete or lost follow-up data after the TACE procedure.

COVID-19 infection

Quantitative reverse transcription-polymerase chain reaction (qRT-PCR) was used as the gold standard test for diagnosing COVID-19 infection. Patients infected with COVID-19 were summarized and graded according to the clinical spectrum of SARS-CoV-2 infection referring to the National Institutes of Health's Coronavirus Disease-COVID-19 Treatment Guidelines (24). COVID-19 infection was characterized by fever, nausea/vomiting, diarrhea, acute respiratory distress syndrome and imaging evidence of respiratory disease. According to the Chinese protocol for the diagnosis and treatment of novel coronavirus pneumonia, patients with COVID-19 were treated with general therapy and antiviral therapy, and patients with severe and critical illnesses were treated with immunotherapy or supportive therapy, as appropriate.

Treatment protocol

Conventional TACE (C-TACE) or TACE with CalliSpheres® microspheres (CSM-TACE) was performed. A 5-F visceral catheter was utilized to catheterize the celiac trunk and the superior mesenteric artery following vascular access through the common femoral artery. Selective arteriography was conducted to identify potential hypervascular tumors. To rule out any possibility of malignant parasitization of blood flow, the potential extrahepatic collateral vessels were carefully examined. Afterwards, a reliable 2.7-F coaxial microcatheter system (Progreat, Terumo, Tokyo, Japan) was successfully inserted into the tumor-feeding arteries.

For C-TACE, the agent for chemoembolization comprised of a mixture of 5–20 mL Ultra-Fluid Lipiodol (Lipiodol Ultrfluido, Guerbet, Paris, France) combined with 50 mg lobaplatin or 2–3 mg raltitrexed. This was followed by embolization utilizing embolic materials (gelatin sponge particles with a diameter of 300–500 μm).

For CSM-TACE, the drug carrier and embolization agent were CalliSpheres® Beads (Jiangsu Hengrui Medicine Co. Ltd., Jiangsu, China), with diameters ranging from 100–300 or 300–500 μm, which were loaded with epirubicin (40 mg).

Follow-up

Selected patients underwent comprehensive laboratory tests, including alpha fetoprotein (AFP), total bilirubin (TBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), platelet (PLT), platelet/lymphocyte ratio (PLR) and neutrophil/lymphocyte ratio (NLR), at 3–7 days and 4–6 weeks after the procedure. Contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) were also performed after 3 months to evaluate the

short-term effect of treatment.

Outcomes

The primary endpoint of the study was safety and risk factors for the emergence of SAEs. Secondary endpoint was objective response rate (ORR) as evaluated based on RECIST 1.1 at the time point of 3 months. The ORR was defined as the sum of complete response (CR) and partial response (PR). All AEs and SAEs were codified and summarized using the Medical Dictionary for Regular Activities (MedDRA) version 22.0 (25) and graded based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 (26). AEs were defined as any unfavorable and unintended signs (including abnormal laboratory findings), symptoms, or diseases. These events may or may not be associated with TACE. SAEs were defined as having an event that results in additional therapy, including an increased level of care, readmission or prolonged hospital stay, a life-threatening condition (cardiopulmonary arrest, shock and organ failure) and even death. AEs of special interest, including respiratory system diseases and venous thromboembolism (VTE), were evaluated, and the incidence rate was recorded. The postembolization syndrome usually presents with fever, nausea or vomiting, and pain. The syndrome by itself was not considered an AE, but rather an expected outcome of embolization. To identify the risk factors that might predict the SAEs occurrence, the following variables were analysed: gender, age, infection status, clinical spectrum of COVID-19 infection, pathogeny, ECOG score, American Society of Anesthesiologists (ASA) status, Child-Pugh class, BCLC stage, number of TACE, tumor size, tumor number, tumor distribution, AFP, TBIL, ALT, AST, PLT, PLR, NLR and tumor response.

Statistical analysis

Categorical data were expressed as number of patients (percentage). Continuous data were expressed as mean ± standard deviation and median (range) for normally and nonnormally distributed variables, respectively. The Wilcoxon signed-rank test, Pearson Chi-squared test, and Fisher exact test were utilized to compare variables, depending on the nature of the data. A multivariate stepwise logistic regression model was used to identify the independent prognostic factors by entering variables associated ($P \leq 0.10$) with SAEs at univariate analysis. The adjusted relative risk [odds ratio (OR)] and 95% confidence interval (CI) were calculated for each independent predictive factor. The statistical analyses were performed using software (SPSS, version 29.0; SPSS Inc., Chicago, Illinois, USA). Statistically differences were defined as a two-tailed P value less than 0.05.

Results

Patient characteristics

A total of 177 patients were screened for eligibility between November 2022 and February 2023. Of these patients, 21 were excluded due to the concurrent systemic or other locoregional therapies in addition to TACE during the study period, 15 cases without COVID-19 testing were also excluded. Another 23 patients were excluded in this study for different reasons. Eventually, 118 patients were enrolled in this study (*Figure 1*). Patients were divided into the infected group (n=73) and the uninfected group (n=45), based on whether they had been diagnosed with concurrent COVID-19 infection or not. The infected group was then divided into three subgroups according to the timing of infection. The subgroups were as follows: patients who had COVID-19 infection within 2 weeks before TACE but recovered or tested negative pre-procedurally (intra-procedural negative group, n=24), patients who had COVID-19 infection within 2 weeks before TACE and were still symptomatic or tested positive pre-procedurally (intra-procedural positive group, n=24), patients who tested negative both within 2 weeks before TACE and pre-procedurally but tested positive within 2 weeks after TACE (post-procedural positive group, n=25).

There were no statistically differences in baseline characteristics between the infected group and the uninfected group. *Table 1* shows the demographic and baseline characteristics of included patients.

Clinical spectrum of COVID-19 infection

As shown in *Table 2*, patients in the infected group were classified as mild (80.8%, 59/73), moderate (13.7%, 10/73), severe (1.4%, 1/73), and critical (4.1%, 3/73). A statistically difference was observed in the severity of COVID-19 between both the intra-procedural positive group and the post-procedural positive group compared to the intra-procedural negative group (P=0.04 and P=0.03, respectively). In the intra-procedural positive group and

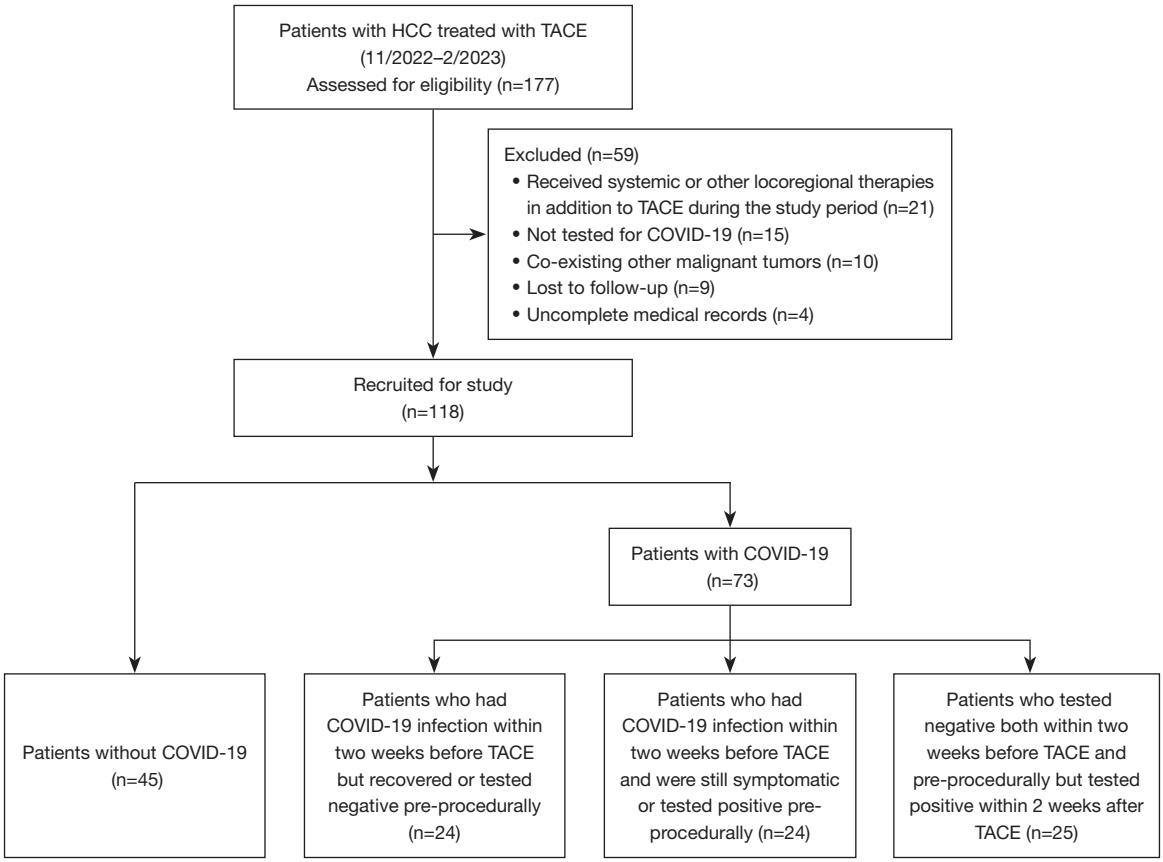

Figure 1 Patient flowchart. HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; COVID-19, coronavirus disease 2019.

Table 1 Demographic and clinical characteristics of patients between the two groups and the subgroups of the infected group

Variables	Total (n=118)	Uninfected group (n=45)	Infected group (n=73)	P value[#]	Infected group (n=73)		
					Intra-procedural negative group (n=24)	Intra-procedural positive group (n=24)	Post-procedural positive group (n=25)
Gender				0.37			
Male	99 (83.9)	36 (80.0)	63 (86.3)		20 (83.3)	21 (87.5)	22 (88.0)
Female	19 (16.1)	9 (20.0)	10 (13.7)		4 (16.7)	3 (12.5)	3 (12.0)
Age, years	55.9±12.4	54.5±12.7	56.8±12.3	0.91	57.2±12.3	58.0±12.1	55.2±12.8
Pathogeny				0.94			
HBV-related	78 (66.1)	31 (68.9)	47 (64.4)		16 (66.7)	15 (62.5)	16 (64.0)
HCV-related	4 (3.4)	1 (2.2)	3 (4.1)		0 (0.0)	1 (4.2)	2 (8.0)
Others	36 (30.5)	13 (28.9)	23 (31.5)		8 (33.3)	8 (33.3)	7 (28.0)
Tumor size, cm	6.8±4.2	7.9±4.6	6.2±3.9	0.27	6.2±4.2	6.8±4.2	5.7±3.5
Tumor distribution				0.55			
Single lobe	80 (67.8)	32 (71.1)	48 (65.8)		14 (58.3)	17 (70.8)	17 (68.0)
Double lobe	38 (32.2)	13 (28.9)	25 (34.2)		10 (41.7)	7 (29.2)	8 (32.0)

Table 1 *(continued)*

Table 1 *(continued)*

Variables	Total (n=118)	Uninfected group (n=45)	Infected group (n=73)	P value[#]	Infected group (n=73)		
					Intra-procedural negative group (n=24)	Intra-procedural positive group (n=24)	Post-procedural positive group (n=25)
Tumor number				0.03			
1	51 (43.2)	18 (40.0)	33 (45.2)		12 (50.0)	10 (41.7)	11 (44.0)
2	27 (22.9)	16 (35.6)	11 (15.1)		1 (4.2)	5 (20.8)	5 (20.0)
≥3	40 (33.9)	11 (24.4)	29 (39.7)		11 (45.8)	9 (37.5)	9 (36.0)
ECOG score				0.76			
0	74 (62.7)	29 (64.4)	45 (61.6)		15 (62.5)	13 (54.2)	17 (68.0)
1	44 (37.3)	16 (35.6)	28 (38.4)		9 (37.5)	11 (45.8)	8 (32.0)
ASA status				>0.99			
1–2	111 (94.1)	42 (93.3)	69 (94.5)		23 (95.8)	23 (95.8)	23 (92.0)
3–4	7 (5.9)	3 (6.7)	4 (5.5)		1 (4.2)	1 (4.2)	2 (8.0)
BCLC stage				0.73			
A	6 (5.1)	2 (4.4)	4 (5.5)		1 (4.2)	0 (0)	3 (12.0)
B	44 (37.3)	19 (42.2)	25 (34.2)		12 (50.0)	6 (25.0)	7 (28.0)
C	68 (57.6)	24 (53.3)	44 (60.3)		11 (45.8)	18 (75.0)	15 (60.0)
Child-Pugh class				0.07			
A	87 (73.7)	29 (64.4)	58 (79.5)		21 (87.5)	18 (75.0)	19 (76.0)
B	31 (26.3)	16 (35.6)	15 (20.5)		3 (12.5)	6 (25.0)	6 (24.0)
Types of TACE				0.62			
C-TACE	48 (40.7)	17 (37.8)	31 (42.5)		10 (41.7)	9 (37.5)	12 (48.0)
CSM-TACE	70 (59.3)	28 (62.2)	42 (57.5)		14 (58.3)	15 (62.5)	13 (52.0)
Number of TACE				0.85			
1	96 (81.4)	37 (82.2)	59 (80.8)		16 (66.7)	20 (83.3)	23 (92.0)
2	22 (18.6)	8 (17.8)	14 (19.2)		8 (33.3)	4 (16.7)	2 (8.0)
AFP, ng/mL				0.53			
<200	75 (63.6)	27 (60.0)	48 (65.8)		18 (75.0)	15 (62.5)	15 (60.0)
≥200	43 (36.4)	18 (40.0)	25 (34.2)		6 (25.0)	9 (37.5)	10 (40.0)
TBIL, μmol/L	19.3±14.2	18.1±10.2	20.1±16.2	0.85	14.5±4.7	16.1±9.1	29.2±23.6
ALT, μ/L	43.9 ±51.4	41.5±52.8	45.4±50.9	0.28	39.2±29.0	43.2±56.3	53.4±61.9
AST, μ/L	53.7±45.6	52.2±40.4	54.6±48.8	0.48	52.2±44.8	50.3±39.6	61.0±60.6
PLT, $\times10^9$/L	132.9±69.9	127.4±66.3	136.3±72.3	0.80	139.3±54.1	118.6±55.6	150.4±96.9
PLR	134.9±92.9	120.5±70.6	143.8±103.8	0.17	170.2±157.4	127.3±59.9	134.1±63.5
NLR	3.4±7.5	2.6±2.3	4.0±9.4	0.13	2.9±2.0	2.8±1.6	6.2±15.8

Data are numbers of patients, with percentages in parentheses, or means ± standard deviations. [#], P value, the infected group *vs*. the uninfected group. HBV, hepatitis B virus; HCV, hepatitis C virus; ECOG, Eastern Cooperative Oncology Group; ASA, American Society of Anesthesiologists; BCLC, Barcelona Clinic Liver Cancer; TACE, transarterial chemoembolization; C-TACE, conventional TACE; CSM-TACE, TACE with CalliSpheres® microspheres; AFP, alpha-fetoprotein; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PLT, platelet; PLR, platelet/lymphocyte ratio; NLR, neutrophil/lymphocyte ratio.

Table 2 Clinical spectrum of COVID-19 infection in the infected group and the subgroups of the infected group

Severity[a]	Total (n=73)	Infected group (n=73)			P value			
		Intra-procedural negative group (n=24)	Intra-procedural positive group (n=24)	Post-procedural positive group (n=25)	P^1	P^2	P^3	P^4
Mild	59 (80.8)	23 (95.8)	18 (75.0)	18 (72.0)	0.07	0.04	0.03	>0.99
Moderate	10 (13.7)	1 (4.2)	3 (12.5)	6 (24.0)				
Severe	1 (1.4)	0 (0.0)	0 (0.0)	1 (4.0)				
Critical	3 (4.1)	0 (0.0)	3 (12.5)	0 (0.0)				

Data are numbers of patients, with percentages in parentheses. P^1, comparison between three groups within the infected group; P^2, intra-procedural negative group *vs*. intra-procedural positive group; P^3, intra-procedural negative group *vs*. post-procedural positive group; P^4, intra-procedural positive group *vs*. post-procedural positive group. [a], the severity of illness categories are based on the National Institutes of Health guidelines for COVID-19: (I) mild illness: no dyspnea or abnormal chest imaging but have any of the other symptoms (e.g., fever, headache, cough, sore throat, malaise, myalgia, gastrointestinal, ageusia, anosmia); (II) moderate illness: oxygen saturation 94% or more on room air at sea level during the acute illness but have evidence of lower respiratory tract disease; (III) severe illness: oxygen saturation less than 94% on room air at sea level, respiratory rate more than 30 breaths per minute, evidence of more than 50% lung infiltrates on imaging, or ratio of arterial partial pressure of oxygen to fraction of inspired oxygen less than 300 mmHg; and (IV) critical illness: respiratory failure, septic shock, and/or multiorgan dysfunction. COVID-19, coronavirus disease 2019.

post-procedural positive group, a lower percentage of mild patients was revealed compared to the intra-procedural negative group (75.0% and 72.0% *vs.* 95.8%, respectively), while the percentage of moderate patients was higher than in the intra-procedural negative group (12.5% and 24.0% *vs.* 4.2%, respectively). One (4.0%) severe patient was reported in the post-procedural positive group, while 3 (12.5%) critical patients were reported in the intra-procedural positive group. No statistically difference was observed in the severity of COVID-19 between the infected subgroups (P=0.07), as well as between the intra-procedural positive group and the intra-procedural positive group (P>0.99).

TACE treatment

During this period, a total of 118 patients underwent TACE. Of these 118 patients, 48 received C-TACE and 70 patients received CSM-TACE. The median number of TACE during the study period was 1 (range, 1–2). A total of 96 of 118 (81.4%) patients received one TACE procedure and 22 of 118 (18.6%) patients received two TACE procedures.

Laboratory tests and tumor response

The clinical data of the two groups and the subgroups of the infected group during hospitalization and follow-up are shown in *Table 3*. No statistically differences were observed in all variables between the infected group and the uninfected group at 3–7 days post-procedurally and 4–6 weeks follow-up. In total, the proportion of patients with high AFP levels (≥200 ng/mL) at 4–6 weeks follow-up was lower than baseline. ALT, AST, PLR and NLR were transiently elevated post-procedurally and recovered at 4–6 weeks. TBIL at 3–7 days and 4–6 weeks after the procedure was slightly higher than baseline. PLT decreased at 3–7 days after the procedure and recovered at 4–6 weeks follow-up. Postembolization syndrome, such as fever, abdominal pain, nausea and vomiting, occurred in most patients, and improved with symptomatic treatment.

In the third month tumor response among all patients (*Table 4*), ORR reached 36.4%, including 39.7% in the infected group and 31.1% in the uninfected group (P=0.43). A total of 90.7% of patients achieved disease control rate (DCR), including 89.0% in the infected group and 93.3% in the uninfected group (P=0.53).

Safety

AEs were reported in all patients (*Table 5*). Fever (78.0%, 92/118), abdominal pain (77.1%, 91/118) and nausea/vomiting (61.9%, 73/118) were the most common AEs of any grade. The incidence of fever (84.9% *vs.* 66.7%), respiratory system diseases (11.0% *vs.* 0.0%) and debilitation (46.6% *vs.* 37.8%) were found higher in the infected group than in the uninfected group. Notably, 4 (3.4%, 4/118) patients experienced gastrointestinal system

Table 3 Clinical examinations of the two groups and the subgroups of the infected group during the hospitalization and follow-up

Variables	Total (n=118)	Uninfected group (n=45)	Infected group (n=73)	P value[#]	Infected group (n=73)		
					Intra-procedural negative group (n=24)	Intra-procedural positive group (n=24)	Post-procedural positive group (n=25)
AFP, ng/mL				0.60			
<200	82 (69.5)	30 (66.7)	52 (71.2)		21 (87.5)	15 (62.5)	16 (64.0)
≥200	36 (30.5)	15 (33.3)	21 (28.8)		3 (12.5)	9 (37.5)	9 (36.0)
TBIL, μmol/L							
3–7-day	24.8±24.1	23.5±20.6	25.5±26.1	0.92	23.5±33.9	19.8±13.8	32.8±26.4
4–6-week	26.1±45.1	30.5±55.8	22.8±35.9	0.724	15.6±10.7	29.4±55.8	23.1±22.9
ALT, μ/L							
3–7-day	80.9±109.5	78.6±99.9	82.4±115.8	0.43	72.1±88.0	49.1±30.2	123.0±168.8
4–6-week	37.3±38.5	33.9±30.0	39.8±43.7	0.63	58.0±69.6	28.3±13.1	33.3±21.1
AST, μ/L							
3–7-day	91.7±87.7	94.3±93.6	90.1±84.6	0.41	82.7±66.6	76.3±63.9	109.5 ±111.5
4–6-week	62.1±96.4	57.1±62.7	65.5±74.3	0.97	81.2±89.3	58.1±66.9	57.3±66.7
PLT, $\times10^9$/L							
3–7-day	113.4±71.6	108.2±66.9	116.6±74.6	0.60	124.9±61.4	105.6±73.7	119.3±86.8
4–6-week	133.3±56.2	133.8±60.7	133.1±54.0	0.95	135.0±45.8	123.2±64.8	141.1±50.6
PLR							
3–7-day	180.7±116.0	172.9±139.1	185.6±99.2	0.11	204.6±104.9	175.2±92.0	179.4±103.4
4–6-week	149.6±78.2	141.3±86.5	155.4±72.4	0.19	162.1±87.1	139.5±61.3	167.4±69.2
NLR							
3–7-day	7.1±6.7	5.9±4.9	8.0±7.6	0.12	6.7±4.7	8.6±6.0	8.5±10.6
4–6-week	3.5±3.4	3.0±2.4	3.9±3.9	0.17	3.7±3.8	4.6±5.0	3.2±2.3

Data are numbers of patients, with percentages in parentheses, or means ± standard deviations. [#], P value, the infected group *vs*. the uninfected group. AFP, alpha-fetoprotein; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PLT, platelet; PLR, platelet/lymphocyte ratio; NLR, neutrophil/lymphocyte ratio.

Table 4 Tumor response at the time point of 3 months by RECIST 1.1

Variables	Total (n=118)	Uninfected group (n=45)	Infected group (n=73)	P value[#]	Infected group (n=73)		
					Intra-procedural negative group (n=24)	Intra-procedural positive group (n=24)	Post-procedural positive group (n=25)
ORR	43 (36.4)	14 (31.1)	29 (39.7)	0.43	11 (45.8)	8 (33.3)	10 (40.0)
DCR	107 (90.7)	42 (93.3)	65 (89.0)	0.53	22 (91.7)	20 (83.3)	23 (92.0)
CR	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)
PR	43 (36.4)	14 (31.1)	29 (39.7)		11 (45.8)	8 (33.3)	10 (40.0)
SD	64 (54.2)	28 (62.2)	36 (49.3)		11 (45.8)	12 (50.0)	13 (52.0)
PD	11 (9.3)	3 (6.7)	8 (11.0)		2 (8.3)	4 (16.7)	2 (8.0)

Data are numbers of patients, with percentages in parentheses. [#], P value, the infected group *vs*. the uninfected group. RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; ORR, objective response rate; DCR, disease control rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 5 Adverse events and serious adverse events in HCC patients after TACE

Adverse events	Total (n=118)	Uninfected group (n=45)	Infected group (n=73)	P value[#]	Infected group (n=73)		
					Intra-procedural negative group (n=24)	Intra-procedural positive group (n=24)	Post-procedural positive group (n=25)
Fever	92 (78.0)	30 (66.7)	62 (84.9)	0.054	17 (70.8)	19 (79.2)	24 (96.0)
Grade 3	2 (1.7)	–	2 (2.7)		–	1 (4.2)	1 (4.0)
Abdominal pain	91 (77.1)	34 (75.6)	57 (78.1)	0.75	20 (83.3)	16 (66.7)	21 (84.0)
Grade 3	1 (0.9)	–	1 (1.4)		–	–	1 (4.0)
Gastrointestinal system diseases	4 (3.4)	1 (2.2)	3 (4.1)	>0.99	0 (0.0)	0 (0.0)	3 (12.0)
Grade 3	2 (1.7)	1 (2.2)	1 (1.4)		–	–	1 (4.0)
Respiratory system diseases	8 (6.8)	0 (0.0)	8 (11.0)	0.02	1 (4.2)	3 (12.5)	4 (16.0)
Grade 3	5 (4.2)	–	5 (6.8)		–	1 (4.2)	4 (16.0)
Grade 5	2 (1.7)	–	2 (2.7)		1 (4.2)	1 (4.2)	–
Liver function injure	3 (2.5)	0 (0.0)	3 (4.1)	0.29	–	2 (8.3)	1 (4.0)
Grade 3	2 (1.7)	1 (2.2)	1 (1.4)		–	–	1 (4.0)
Grade 4	1 (0.9)	–	1 (1.4)		–	1 (4.2)	–
VTE	1 (0.9)	0 (0.0)	1 (1.4)	>0.99	0 (0.0)	1 (4.2)	0 (0.0)
Grade 5	1 (0.9)	–	1 (1.4)		–	1 (4.2)	–
Nausea/vomiting	73 (61.9)	28 (62.2)	45 (61.6)	0.95	16 (66.7)	12 (50.0)	17 (68.0)
Debilitation	51 (43.2)	17 (37.8)	34 (46.6)	0.35	13 (54.2)	10 (41.7)	11 (44.0)
SAE	16 (13.6)	2 (4.4)	14 (19.2)	0.046	1 (4.2)	5 (20.8)	8 (32.0)
Fever	2 (1.7)	–	2 (2.7)		–	1 (4.2)	1 (4.0)
Abdominal pain	1 (0.9)	–	1 (1.4)		–	–	1 (4.0)
Gastrointestinal system diseases	2 (1.7)	1 (2.2)	1 (1.4)		–	–	1 (4.0)
Respiratory system diseases	7 (5.9)	–	7 (9.6)		1 (4.2)	2 (8.3)	4 (16.0)
Liver function injure	3 (2.5)	1 (2.2)	2 (2.7)		–	1 (4.2)	1 (4.0)
VTE	1 (0.9)	–	1 (1.4)		–	1 (4.2)	–

Data are numbers of patients, with percentages in parentheses. [#], P value, the infected group *vs*. the uninfected group. HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; VTE, venous thromboembolism, SAE, serious adverse event.

diseases after the procedure [3 (4.1%) of 73 patients in the infected group *vs.* 1 (2.2%) of 45 patients in the uninfected group]. Additionally, 3 (2.5%, 3/118) patients had liver function injury [3 (4.1%) *vs.* none]. There was also one patient (0.9%, 1/118) with VTE [1 (1.4%) *vs.* none]. The incidence of respiratory system disease was statistically different between the infected group and the uninfected group (P=0.02). There was no statistically difference in the incidence of other AEs between the two groups.

In addition, 16 (13.6%, 16/118) patients experienced SAEs (*Table 5*). Among them, 14 (19.2%) of 73 patients were in the infected group and two (4.4%) of the 45 patients were in the uninfected group (P=0.046). The most common SAEs were respiratory system diseases (43.8%, 7/16), liver function injury (18.8%, 3/16), fever (12.5%, 2/16) and gastrointestinal system diseases (12.5%, 2/16). Twelve (10.2%, 12/118) patients experienced grade 3 AEs [10 (13.7%) of 73 in the infected group *vs.* 2 (4.4%) of 45 in the uninfected group], which included five with respiratory system diseases, two with fever, one with abdominal

Table 6 Results of univariate and multivariate analysis of factors associated with SAEs

Parameters	Univariate analysis[#]			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
Gender	2.857	0.862–9.468	0.09	1.604	0.280–9.204	0.60
Age	1.061	1.007–1.118	0.03	1.064	1.002–1.131	0.044
Infection status	5.102	1.102–23.627	0.04	0.444	0.046–4.314	0.48
Clinical spectrum of COVID-19	4.259	1.943–9.336	<0.001	5.736	1.772–18.568	0.004
Pathogeny	0.974	0.546–1.738	0.93			
ECOG score	0.796	0.186–3.403	0.76			
ASA class	2.771	0.490–15.678	0.25			
Child-Pugh class	0.360	0.077–1.682	0.19			
BCLC stage	0.921	0.383–2.213	0.85			
Number of TACE	0.586	0.123–2.788	0.50			
Tumor size	0.959	0.839–1.095	0.53			
Tumor number	0.784	0.422–1.458	0.44			
Tumor distribution	0.442	0.118–1.654	0.23			
AFP	0.327	0.064–1.671	0.18			
TBIL	1.016	0.985–1.048	0.32			
ALT	0.994	0.977–1.011	0.47			
AST	0.999	0.986–1.011	0.81			
PLT	1.001	0.993–1.008	0.89			
PLR	1.002	0.997–1.006	0.53			
NLR	1.053	0.976–1.137	0.18			
ORR	0.358	0.096–1.335	0.13			

[#], variables with P value ≤0.10 in the univariate analysis were further included in the multivariate logistic proportional hazards regression model analysis. SAE, serious adverse event; OR, odds ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ASA, American Society of Anesthesiologists; BCLC, Barcelona Clinic Liver Cancer; TACE, transarterial chemoembolization; AFP, alpha-fetoprotein; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PLT, platelet; PLR, platelet/lymphocyte ratio; NLR, neutrophil/lymphocyte ratio; ORR, objective response rate.

pain, one with gastrointestinal system diseases, one with liver function injury in the infected group, one with gastrointestinal system diseases (peptic ulcer) and one with liver function injury in the uninfected group. One (0.9%, 1/118) patient experienced grade 4 liver function injury [1 (1.4%) *vs.* none]. AEs that led to death (grade 5) occurred in 3 (2.5%, 3/118) patients [3 (4.1%) *vs.* none], which included two respiratory system diseases (respiratory failure) and one of VTE [pulmonary thromboembolism (PTE)].

Risk factors for severe AEs

In the univariate analysis, infection status (P=0.04), gender (P=0.09), age (P=0.03) and clinical spectrum of COVID-19 (P<0.001) were considered as the potential risk factors of grade ≥3 AEs. In the multivariate analysis, only age (P=0.044) and clinical spectrum of COVID-19 (P=0.004) showed significance for SAEs after adjustment for other variables (*Table 6*). Patients with more severe COVID-19 and elderly patients were more likely to experience SAEs after TACE.

Discussion

To our knowledge, this study is the first to investigate the safety of TACE in HCC patients with COVID-19, which is

currently a relatively common phenomenon. This research demonstrated that all HCC patients who had COVID-19 infection and treated with TACE experienced one or more AEs of varying severity. Of note, in the infected subgroups, patients infected with COVID-19 within 2 weeks before TACE and tested negative or improved pre-procedurally had almost the same incidence of AEs and SAEs as those who did not have COVID-19 infection. Furthermore, patients who did not show improvement of COVID-19 at the time of TACE and those who developed COVID-19 infection after TACE procedure experienced higher rates of AEs and SAEs compared to patients who were not infected. Some of these events may be attributed to COVID-19, emphasizing the importance of giving extra attention to COVID-19 infection in these patients. Only 16 (13.6%, 16/118) patients encountered SAEs. The incidence of SAEs in the infected group was higher than that in the uninfected group, which may have a direct impact on the postoperative monitoring and nursing care of HCC patients with COVID-19.

Two risk factors appeared to promote SAEs in our cohort of patients. One factor was older age. Previous studies suggest that older age may not affect the safety of TACE (27-29), but is associated with more severe COVID-19 disease (11,30-33). Generally, elderly patients tend to have a higher proportion of comorbidities compared to younger patients, and this could potentially increase the risk of complications related to TACE (28). In this study, we demonstrated the association between older age and postprocedural SAEs in HCC patients with periprocedural COVID-19 infection, which emphasized the importance of age as a prognostic factor for HCC patients coinfected with COVID-19 after TACE.

Another factor that could lead to the SAEs occurrence was the clinical spectrum of COVID-19. Currently, no previous research has been conducted to discuss the association between the clinical spectrum of COVID-19 and the safety of performing TACE in HCC patients with COVID-19. In this research, the occurrence of SAEs seemed to be higher in the subgroups with a greater proportion of moderate or more severe COVID-19, which may demonstrate a notable association between the severity of COVID-19 and the risk of SAEs.

This study presents a deviation from previous research that demonstrated the increased incidence of postoperative respiratory complications (23.0–51.2%) among patients with perioperative COVID-19 infection (30,34,35). Our study demonstrated that the rate of respiratory system diseases was 11.0% in the infected group. The rate was found to be lower compared to that stated in the previous studies. This may be due to the fact that the Omicron SARS-CoV-2 variant which was prevalent during the study period was associated with less severe clinical illness compared to earlier variants (36-38).

Previous studies identified a higher postoperative mortality (20.5–23.8%) in patients with perioperative COVID-19 infection undergoing surgery treatment, and the majority of the mortality was from respiratory system complications (82.6–100%), such as acute respiratory distress syndrome or respiratory failure (30,34), which was different from our study. In this research, a lower post-procedure mortality was observed (4.1%, 3/73). Among the patients who died, 2 (66.7%, 2/3) patients died of respiratory failure, accounting for 20.0% (2/8) of patients with respiratory complications. One patient (33.3%, 1/3) died as a result of PTE, accounting for 1.4% (1/73) of patients infected with COVID-19, a rate that is similar to the reported postoperative VTE rates of 1.6–2.2% in an international prospective cohort study (39). One possible reason may be that TACE played a different role in the occurrence of severe AEs compared to open surgery for perioperative patients with COVID-19. On the other hand, several studies have confirmed that COVID-19 was associated with an increased incidence of VTE (40-44). Thus, for patients with COVID-19 infection, it is necessary to identify the potential prodromal symptoms and take appropriate precautions to protect patients from the development of VTE.

In most Western countries, many medical procedures, including some loco-regional treatments, were postponed during COVID-19 to reduce immunosuppression risks (7,8). A notable case report highlighted a patient with advanced HCC who, after being vaccinated against COVID-19 and receiving systemic therapy with atezolizumab and bevacizumab, experienced spontaneous regression of the cancer. This phenomenon may suggest a complex interplay involving immune modulation (45). Furthermore, Ma *et al.* (46) demonstrated that postoperative adjuvant TACE could enhance survival outcomes and address immune status imbalances in HCC patients with microvascular infiltration. During the last years, increasing evidence supports the potential benefits of combining systemic therapeutic agents with TACE (47,48). However, for HCC patients who have contracted COVID-19, it is still uncertain whether postoperative adjuvant TACE therapy can effectively mitigate immunosuppression following resection and

whether TACE combined with systemic therapy can significantly enhance the immune-mediated antitumor response remains to be fully explored. Further research is required to address these questions.

There were several limitations in our study. Firstly, both the C-TACE and CSM-TACE were performed in HCC patients. Thus, the effects of the different types of TACE on the safety of HCC patients with COVID-19 could not be determined. It is essential to conduct additional investigations to explore this aspect further. Secondly, the focus of this research was the safety of TACE in patients with COVID-19 on short-term observation. The impact of COVID-19 infection in HCC patients receiving TACE on overall survival or progression free survival needs to be explained in a future study with longer intervals and more follow-up visits. The patients enrolled in this study were still under close follow-up. Lastly, the possibility of selection bias is inevitable due to the retrospective study design.

Conclusions

In summary, the safety of TACE in HCC patients with peri-procedural COVID-19 was deemed acceptable compared to open surgery and delaying TACE was unnecessary. Age and the clinical spectrum of COVID-19 were correlated with SAEs. It is important to note that HCC patients with COVID-19 may be more likely to develop AEs or SAEs. Postoperative care and symptomatic treatment are crucial for HCC patients with COVID-19 undergoing TACE.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-527/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-527/dss

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-527/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-527/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology approved this retrospective study (IORG No. IORG0003571). Each participant provided their consent to participate.

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Cite this article as: Wang Z, Yang T, Zhang L, Makamure J, Hong W, Liang B. Age and clinical spectrum of COVID-19 are associated with safety of transarterial chemoembolization in hepatocellular carcinoma: a retrospective cohort study. J Gastrointest Oncol 2024;15(6):2642-2655. doi: 10.21037/jgo-24-527

